REMARKS/ARGUMENTS

Claims 1-4, 6-24 and 26-40 are pending. Claims 1, 21 and 27 have been amended herein. Claims 5 and 25 have been cancelled without intending to abandon or to dedicate to the public any patentable subject matter. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of the claims are respectfully requested.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 1, 5 and 10 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,849,240 (hereinafter "**Miller**"). Miller teaches a single dosage form containing morphine sulfate, poloxamer 188 and magnesium stearate (see Table V). (It should be noted that Miller teaches the use of magnesium stearate, a tableting excipient, and not magnesium sulfate, a saline laxative). Applicants have cancelled Claim 5 and amended Claim 1 to define the stool softener more narrowly. As a result of these amendments, Miller does not anticipate the pending claims.

The Examiner has also rejected Claims 1, 5 and 10 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,181,719 (hereinafter "**Margetts**"). Margetts discloses a single dosage form containing acetaminophen, codeine and docusate (see Formulation 3, in Column 15). This reference teaches that the docusate is present at only 1.7mg per tablet (see Column 17, lines 1-2). Thus, it would appear that the docusate is present as an excipient to aid in tableting or dissolution and the disclosed composition does not anticipate any of Claims 1-11, which do not name codeine, nor does it anticipate any of Claims 12-20 as it does not contain at least about 50mg of docusate.

The Examiner has also rejected Claims 1, 2, 5 and 10 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,599,342 (hereinafter "**LaHann**"). LaHann describes an

analgesic composition containing codeine or propoxyphene, N-vanillyl-9E-octadecenamide (a non-opiate analgesic) and methylcellulose (see Examples I and II in Column 8). The analgesic composition of LaHann does not anticipate Claims 1, 2, 5 and 10 as these claims do not recite codeine.

The Examiner has also rejected Claims 1, 5, 10, 21 and 25 under 35 U.S.C. § 102(b) as being anticipated by GB Patent No. 2 281 205 (hereinafter "**Brown**"). Brown teaches a composition containing an opioid and bisacodyl. Applicants have cancelled Claims 5 and 25. Applicants have amended Claims 1 and 21 to more narrowly define the stool softener. Thus, Claims 1, 10 and 21, as amended, are not anticipated by Brown.

Applicants therefore respectfully request the Examiner's rejections under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected Claims 1, 5, 8-12, 16-19, 21, 25, 28-30, 33 and 37-39 under 35 U.S.C. § 103(a) as being obvious over Lazarus, H. et al., A Multi-Investigator Clinical Evaluation of Oral Controlled-Release Morphine (MS Contin® Tablets), Hospice Journal, 6(4):1-15 (1990) (hereinafter "Lazarus") and the description of Senokot-S® tablets from the drugs.com web site.

The Examiner notes that Senokot-S® (SKS) tablets contain 8.6mg of sennosides and 50 mg of docusate as shown by the web site listing and that Lazarus teaches the administration of SKS tablets in combination with MS Contin® to prevent opioid related constipation. The Examiner argues that the combination of an opioid and docusate in a single solid dosage form would have been obvious as a mere judicious choice of ingredients given that Lazarus teaches that the simultaneous administration of sennosides, docusate and morphine to reduce the frequency of constipation in patients.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Lazarus teaches the use of sustained-release oral morphine to treat chronic pain. The morphine dosage for the patients studied was varied between 30mg every 12 hours up to greater than 90mg every 12 hours. However, over this morphine dosage range, the docusate dosage (as part of the laxative combination in the SKS tablets) only ranged from 150mg to 250mg. Thus, there is a non-linear increase in the dosage of docusate and opioid amongst the patients studied in the Lazarus article. Indeed, as shown in Figure 1 of Lazarus, at the two doses taken by the majority of the study participants (1 tablet every 12 hours or 2 tablets every 12 hours) the amount of docusate was the same, or actually lower, at the higher dosage of morphine. But this non-linear increase in docusate dosage, or even decrease in the docusate dosage, with a corresponding increase in morphine dosage would not have been possible using the single solid dosage form claimed in the instant application that would require a doubling of the docusate dose with every doubling of the morphine dose. Instead, the patients described in Lazarus used dosages from 2 tablets per day, to 4 tablets per day, to 8 or more tablets per day while only showing an increase in docusate use from 150mg to 250mg (i.e. never doubling the docusate dosage even once). Thus, one of skill in the art of pharmaceuticals that read and understood the Lazarus article would not have been motivated to combine morphine (or an equivalent opioid) with docusate in a single solid dosage form because this ability to separately titrate the docusate dosage independent of the morphine dosage, noted to be so effective by Lazarus, would not have been possible with such single solid dosage form. That is, the data gathered and highlighted as particularly advantageous in the administration of an opioid in Lazarus could not have been replicated with the single dosage forms recited in the presently pending claims. Thus, Lazarus teaches away from the use of the single dosage forms of the present invention and even the use of any single dosage form containing a laxative (or laxative combination) with an opioid that, by definition, will not allow

the titration of the opioid dose separate from the dose of the laxative and specifically will not allow doubling or quadrupling of the opioid dose without doubling of the dose of the laxative(s) contrary to the teachings of Lazarus.

Therefore, the Lazarus article does not suggest the use of a single solid dosage form as argued by the Examiner, but instead teaches the use of separate dosage forms allowing separate dosage titration of the opioid and the laxatives. Thus, there is no motivation in the references or reasonable expectation of success based on the Lazarus research to combine the references, and Applicants submit that the obviousness rejection based on this combination of references should be withdrawn.

The Examiner has also rejected Claims 1-5, 8-25 and 28-40 as obvious in light of **Lazarus** taken in combination with:

Raeder, J.C. et al. Anesthesia & Analgesia 92(6):1429-45 (2001) ("Raeder"),

Mullican, W.S. et al. Clinical Therapeutics 23(9):1429-1445 (2001) ("Mullican"),

Marketletter entitled "U.S. Seniors Surveyed on Pain Relief" published July 1997 ("Marketletter"),

Maurer, A.H. et al. J. Of Nuclear Medicine 37(5):818-822 (1996) ("Maurer"), and

Rauck, R.L. et al. Current Therapeutic Research-Clinical and Experimental 55(4):1417-31 (1994) ("Rauck").

The Examiner cites Reader, Mullican, Marketletter, Maurer and Rauck as teaching the combination of codeine and acetaminophen and the fact that this combination of drugs is associated with the adverse effect of constipation. Thus, the Examiner argues that it would have been obvious to use the opiate codeine and to include the non-opiate acetaminophen in a single solid dosage form with docusate given these references and the teachings of Lazarus; particularly where the Lazarus article teaches the equivalent dose of codeine to the dosage of morphine. However, as discussed above, the Lazarus article does not suggest the combination of an opioid

with docusate in a single solid dosage form but instead teaches the independent dosage adjustment of laxatives by separate administration of the drugs. None of the Reader, Mullican, Marketletter, Maurer or Rauck references overcomes this shortcoming of the Lazarus reference. Indeed, with respect to Raeder, the reference teaches avoiding the constipation associated with codeine by the administration of ibuprofen in place of the acetaminophen and codeine combination. Therefore, the combination of Lazarus with Reader, Mullican, Marketletter, Maurer and Rauck does not overcome the problems with Lazarus described above and the Examiner's rejections based upon this combination of references should similarly be withdrawn.

The Examiner has also rejected Claims 1, 2-5, 10, 11, 21-25, 30 and 31 as being obvious in light of **Brown and U.S. Patent No. 6,375,957 ("Kaiko")**. As described above, Brown teaches the combination of the stimulant laxative bisacodyl and an opioid. Applicants have cancelled Claims 5 and 25 and have amended Claims 1 and 21 to more narrowly recite the claimed stool softeners. Thus, Brown (and therefore the combination of Brown and Kaiko) does not teach all of the limitations of the instant claims, as amended, and Applicants therefore request that the rejections based on this combination of references be withdrawn.

The Examiner has rejected Claims 1-40 as being obvious in light of **Brown and Kaiko in view of U.S. Patent No. 5,232,699 ("Colliopoulos") and U.S. Patent No. 5,516,524 ("Kais")**. The combination of Brown and Kaiko teach combinations of opioids and non-opioid analgesics with the stimulant laxative bisacodyl as described above. The references of Colliopoulos and Kais are cited by the Examiner as teaching psyllium and docusate as having a laxative effect. The Examiner argues that given the teachings of Brown and Kaiko, one of skill in the art, presented with the laxative information in Colliopoulos and Kais, would have found it obvious to substitute either psyllium or docusate in a solid dosage form in place of the bisacodyl of Brown, absent evidence to the contrary.

As stated at page 1 of Brown, the reference discloses the surprising finding that the stimulant laxative bisacodyl, combined with morphine, does not require an enteric coating to overcome the colic and/or abdominal cramping associated with stimulant laxatives. It is therefore possible, according to the Brown disclosure, to administer a stimulant laxative, and particularly bisacodyl, with morphine in a single dosage form that does not contain an enteric coating.

Included with this Amendment and Response is a copy of an excerpt of the chapter reviewing *Laxative Products* from The Handbook of Nonprescription Drugs, seventh edition, by Clarence E. Curry, Jr., published by the American Pharmaceutical Association, 1982. In this excerpt is a description of the mechanism of action of the stimulant laxatives (see pages 76-78), and the bulk-forming and emollient laxatives (see pages 72-75). As noted therein, the diphenyl methane laxative bisacodyl stimulates the mucosal nerve plexus producing contractions of the entire colon. Conversely, the bulk-forming laxatives swell in the intestinal fluid, forming emollient gels that facilitate the passage of intestinal contents and emollient laxatives increase the wetting efficiency of intestinal fluid and facilitate the admixture of aqueous and fatty substances to soften fecal masses. Therefore, one of skill in the art of pharmacology would not expect that any other laxative could simply be substituted in the place of bisacodyl to have the same laxative effect by a different mechanism of action. This is particularly so in the instant case in which the substitution proposed by the Examiner would require the substitution of a laxative that acts by direct stimulation of the colonic nerve plexus with a laxative that acts by emulsifying or softening the stool. Thus, contrary to the Examiner's argument, this evidence shows that one of skill in the art would not have considered bisacodyl to be immediately or obviously replaceable in the dosage form of Brown by any laxative and particularly not by either docusate or phyllium as they exert their laxative effects by entirely different mechanisms.

In making this §103(a) rejection, the Examiner seems, in essence, to be stating that it would have been "obvious to try" modifying the laxative component of Brown, and selecting laxatives having entirely different mechanisms of action, in order to produce the instantly claimed invention. The Federal Circuit has provided clear direction with respect to arguments

based on an "obvious to try" theory. The court has held that an "obvious to try" situation exists when a general disclosure may pique a scientists curiosity, such that further investigation might be done as the result of a disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 14 USPQ 2d 1741, 1743 (Fed.Cir. 1990). The court held, however, that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. See Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ 2d 1923, 1928 (Fed.Cir. 1990). For the foregoing reasons, Applicants respectfully submit that because neither Brown nor Colliopoulos or Kais, alone or in combination, provide sufficient suggestions or teachings to direct one of ordinary skill in the art to make the present invention through substitution of unrelated laxatives, the Examiner should withdraw the §103 rejections predicated upon the combination of these references.

Therefore, Applicants submit that the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,
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6 Laxative Products

Clarence E. Curry Jr.

Questions to Ask the Patient

Why do you feel you need a laxative?

Do you have any abdominal discomfort or pain, bloating, weight loss, nausea, or vomiting?

Are you currently being treated by a physician for any illness?

Have you had any abdominal surgery recently?

How often do you normally have a bowel movement?

How would you describe your bowel movements? Have they changed in any way recently?

Has the appearance of your stools changed? In what way?

How long has constipation been a problem?

Have you used laxatives previously to relieve constipation?

Are you currently taking any medicine other than laxatives?

Are you using a laxative now? How often and how long have you used a laxative?

Have you attempted to relieve the constipation by eating more cereals, bread with a high fiber content, fruits, or vegetables?

How much physical exercise do you get?

How many glasses of water do you drink each day?

Are you allergic to any medicines?

Have you had any unwanted effects from laxatives, such as diarrhea?

Extensive media advertising promotes the idea that having clockwork-like bowel movements in some way enhances well-being and social acceptability. With the general increase in consumer interest in natural products, specifically in treating constipation, overall sales of laxatives in the United States in 1980 increased 10% over the previous year and accounted for one-third of a billion dollars in sales (1). Obviously, not all laxatives are natural products in the pharmaceutical sense nor are "natural" products natural to normal body biochemical and physiologic processes.

Laxative products facilitate the passage and elimination of feces from the colon and rectum (2). There are few recognized medical indications for the use of laxatives, but many people misuse these products to alleviate what they consider to be constipation. Constipation has different meanings for different patients. However, it generally is defined as a decrease in the frequency of fecal elimination characterized by the difficult passage of hard dry stools. It usually results from the abnormally slow movement of feces through the colon with resultant accumulation in the descending colon.

Causes of Constipation

Causes of constipation are numerous (Table 1–5). The main disorders of the colon, ulcerative colitis and excessive parasympathetic stimulation, and the chronic misuse of irritant laxative drugs, may cause constipation or diarrhea. The etiology of colitis remains unknown. Constipation is often a problem in ulcerative colitis patients in whom the disease process is limited to the rectum. Indeed, in an ulcerative colitis patient with diarrhea, the use of antidiarrheal agents can result in colonic dilation or the accumulation of hard stool in an area of bowel not affected by disease (3).

Constipation of organic origin may be due to hypothyroidism, megacolon, stricture, or lesions (benign or malignant). Laxatives are contraindicated in such cases; proper diagnosis and medical treatment should be obtained.

to defecate. It also may be caused by degeneration of nerve pathways concerned with defecation reflexes.

Painful lesions of the anal canal, such as ulcers, fissures, and thrombosed hemorrhoidal veins, impede defecation by causing a spasm of the sphincter and by promoting voluntary suppression of defecation to avoid pain.

The normal rectal mucosa is relatively insensitive to cutting or burning. However, when it is inflamed, it becomes highly sensitive to all stimuli, including those acting on the receptors mediating the stretch reflex. A constant urge to defecate in the absence of appreciable material in the rectum may occur with inflamed rectal mucosa (7).

Symptoms of Constipation

If constipation does occur, complex symptoms of varying degrees may develop. Typical symptoms include anorexia, dull headache, lassitude, low back pain, abdominal distention, and lower abdominal distress. Abdominal discomfort and inadequate response to increasing varieties and doses of laxatives are frequent complaints. Although only limited quantitative data are available, one study indicated that the range of bowel movement frequency in humans is from 3 times/day to 3 times/week (8). These latter individuals are usually symptom-free and do not have any specific abnormality related to their individual pattern of defecation. Therefore, constipation cannot be defined solely in terms of the number of bowel movements in any given period.

Patients have many different concepts of what constipation is (9) and many misconceptions concerning normal bowel functioning (10). Indeed, various definitions of constipation were expressed by participants in a study (9). Despite that, 75% of these persons indicated that they used a laxative when they were constipated. Regardless of how the patient defines constipation, it is likely that a laxative product will be considered to treat it.

Treatment

Constipation that does not have an organic etiology can often be alleviated without the use of a laxative product. The pharmacist should stress the importance of a high-fiber diet, plentiful fluid consumption, and exercise. However, treatment may require recommendation of a laxative.

Pharmacologic Agents

The ideal laxative would be nonirritating and nontoxic, would act only on the descending and sigmoid colon, and would produce a normally formed stool within a few hours. Its action would then cease, and normal bowel activity would resume. Since a laxative that meets these criteria is not presently available, proper selection of such an agent depends upon the etiology of the constipation.

Laxative drugs have been classified according to site of action, intensity of action, chemical structure, or mechanism of action. The most meaningful classification is the mechanism of action, whereby laxatives are classified as bulk forming, emollients, lubricants, saline, and stimulants (Table 6).

Table 4: Disorders of bowel structures associated with constipation

- **Colonic disorders**
  - Obstruction
    - Extraluminal
      - Tumors
      - Chronic volvulus
      - Hernias
      - Rectal prolapse
    - Luminal
      - Tumors
      - Strictures
        - Chronic diverticulitis
        - Chronic amebiasis
        - Lymphogranuloma venereum
        - Syphilis
        - Tuberculosis
        - Ischemic colitis sequelae
        - Endometriosis
        - Corrosive enemas
        - Surgery
  - Functional disorders
    - Mucosal abnormalities
      - Ulcerative proctitis
    - Muscular abnormalities
      - Diverticular disease, irritable colon syndrome
      - Myotonic dystrophy
      - Systemic sclerosis
      - Dermatomyositis
- **Rectal disorders**
  - Rectocele
- **Anal disorders**
  - Mechanical disorders
    - Stenosis
  - Functional disorders
    - Puborectalis syndrome
    - Anal fissure
    - Anal fistulous abscess
    - Mucosal prolapse

Adapted with permission from "Gastrointestinal Disease," J. S. Fordtran and M. Sleisenger, Eds., W. B. Saunders, Philadelphia, Pa., 1978, pp. 370–373.

Bulk-Forming Laxatives

Because they approximate most closely the physiologic mechanism in promoting evacuation, bulk-forming products are the recommended choice as initial therapy for constipation. These laxatives are natural and semisynthetic polysaccharides and cellulose derivatives that dissolve or swell in the intestinal fluid, forming emollient gels that facilitate the passage of the intestinal contents and stimulate peristalsis. They are usually effective in 12–24 hours but may require as long as 3 days in some individuals. This type may be indicated for people on low-residue diets that cannot be corrected as well as in postpartum patients, elderly patients, and patients with irritable bowel syndrome or diverticular disease.

Since they are not absorbed systemically, the hydrophilic colloid laxatives do not seem to interfere with the absorption of nutrients. When given as a powder or granules, they should be mixed with pleasant tasting fluids, such as fruit juice, just before ingestion and administered with a full (8 oz) glass of fluid. Most patients prefer juices or soft drinks over water because they help to avoid the gritty, tasteless sensation of the bulk-forming laxatives. Failure to consume sufficient fluid with the laxative decreases drug efficacy and may result in intestinal or esophageal obstruction. These agents may be inappropriate for patients who must severely restrict their fluid intake, such as those with significant renal disease.

Esophageal obstruction has occurred in patients who have difficulty swallowing, such as those with strictures of the esophagus when these drugs are chewed or taken in dry form. In addition, there have been reports of acute bronchospasm associated with the inhalation of dry hydrophilic mucilloid (11). Because of the danger of fecal impaction or intestinal obstruction, the bulk-forming laxatives should not be taken by individuals with intestinal ulcerations, stenosis, or disabling adhesions. When administered properly, these agents are essentially free from systemic side effects because they are not absorbed.

Bulk-forming laxatives are derived from agar, plantago (psyllium) seed, kelp (alginates), and plant gums [tragacanth, chondrus, karaya (sterculia), and others]. The synthetic cellulose derivatives—methylcellulose and carboxymethyl cellulose sodium—are being used more frequently, and many preparations that contain these drugs also contain stimulant and/or fecal-softening laxative drugs. Although the natural product psyllium appears to be the most popular, the synthetic colloidal materials, including methylcellulose and carboxymethyl cellulose sodium, have a high degree of uniformity and can be readily compressed into tablets. Because they are more convenient to take, the use of these agents is increasing.

Calcium polycarbophil, the calcium salt of a synthetic polyacrylic resin that has a marked capacity for binding water, has been released for the treatment of constipation associated with irritable bowel syndrome and diverticular disease. Since the maximum calcium content of this agent is approximately 150 mg (7.6 mEq) the ingestion of recommended therapeutic dosages may increase the risk of hypercalcemia in susceptible patients. However, the maximum daily dosage limit for calcium adopted by the FDA is considerably higher than the 1,800 mg of calcium contained in the maximum daily dose of 12 calcium polycarbophil tablets (12).

Table 5. Dietary factors associated with constipation

Lack of sufficient bulk in the diet
Excessive ingestion of foods that harden stools, such as processed cheese
Inadequate fluid intake

Adapted with permission from "Gastrointestinal Disease," J. S. Fordtran and M. Sleisenger, Eds., W. B. Saunders, Philadelphia, Pa., 1978, pp. 370–373.

A final member of the bulk forming laxatives is malt soup extract, which is obtained from barley and contains maltose protein and potassium as well as amylolytic enzymes. An interesting aspect of this agent is that it reduces fecal pH, which may contribute to its activity.

One study indicated that a mixture of cellulose and pectin (Phybrex), was equivalent to psyllium as a bulk laxative. The agent had the added advantage of not gelling when mixed with liquids, allowing its usage in baked foods, sauces, drinks, stews, and other recipes. Because of its wider range of methods of consumption, this agent may ensure better compliance over long periods of time (13).

It has been observed that making a specific choice among the different bulk products is relatively unimportant (14). It is more important that each dose be taken with a full glass of water (at least 240 ml, or 8 oz). The sodium and dextrose content of some of the commercial products should be evaluated in patients on sodium and carbohydrate-restricted diets. The dose should be adjusted until the required effect has been obtained. In addition to being relatively safe, bulk-forming laxatives are suitable should long-term therapy become necessary.

Patients with symptoms of cathartic colon from stimulant laxative overuse should be warned that the use of a bulk-forming laxative can result in intestinal obstruction.

Emollient Laxatives

Docusate, formerly known as dioctyl sodium sulfosuccinate, is a surfactant which, when administered orally, increases the wetting efficiency of intestinal fluid and facilitates admixture of aqueous and fatty substances to soften the fecal mass. Docusate does not retard absorption of nutrients from the intestinal tract. In many cases of fecal impaction, a solution of docusate is added to the enema fluid. Docusate and its congeners are claimed to be nonabsorbable, nontoxic, and pharmacologically inert.

Other fecal-softening laxatives are docusate calcium (anionic surfactant), docusate potassium (anionic surfactant), and poloxamer 188 (nonionic surfactant). The latter has no irritant properties and is compatible with electrolytes.

Emollient laxatives should be used only for short-term therapy (less than 1 week without physician consultation) where hard fecal masses are present: either in acute perianal disease in which elimination of painful stools is desired or in which the avoidance of straining at the stool is desirable (following rectal surgery or myocardial infarction).

Orally administered emollient laxatives are of no value in treating constipation of long-term duration, especially in elderly and debilitated patients. One study indicated that the prophylactic administration of doc-

Table 6. Classification and properties of laxatives

Agent	Dosage form	Daily dosage range: Adult	Daily dosage range: Pediatric (age in years)	Site of action	Approximate time required for action	Systemic absorption
Bulk-Forming						
Methylcellulose	Solid	4–6 g	1–1.5 g (>6)	Small and large intestines	12–72 hours	No
Carboxymethyl cellulose sodium	Solid	4–6 g	1–1.5 g (>6)	Small and large intestines	12–72 hours	No (laxative) Yes (sodium)
Malt soup extract	Solid, liquid, powder	12–64g	6–32 oz (1 month–2 year)	Small and large intestines	12–72 hours	—
Polycarbophil	Solid	4–6 g	0.5–1.0 g (<2) 1–1.5 g (2–5) 1.5–3.0 g (6–12)	Small and large intestines	12–72 hours	No
Plantago seeds	Solid	2.5–30 g	1.25–15 g (>6)	Small and large intestines	12–72 hours	No
Emollient						
Dioctyl calcium sulfosuccinate	Solid	0.05–0.36 g	0.025 g (<2) 0.05–0.150 g (≥2)	Small and large intestines	12–72 hours	Yes
Dioctyl sodium sulfosuccinate	Solid	0.05–0.36 g	0.02–0.05 g (<2) 0.05–0.15 g (≥2)	Small and large intestines	12–72 hours	Yes
Dioctyl potassium sulfosuccinate	Solid (rectal)	0.05–0.25 g	0.1 g (children)	Colon	2–15 min	—
Lubricant						
Mineral oil	Liquid (oral)	14–45 ml	10–15 ml (>6)	Colon	6–8 hours	Yes-minimal amount
Saline						
Magnesium citrate	Solid	11–18 g	2.5–5.0 g (2–5)	Small and large intestines	0.5–3 hours	Yes
Magnesium hydroxide	Solid	2.4–4.8 g	0.4–1.2 g (2–5) 1.2–2.4 g (≥6)	Small and large intestines	0.5–3 hours	
Magnesium sulfate	Solid	10–30 g	2.5–5.0 g (2–5) 5.0–10.0 g (6)	Small and large intestines	0.5–3 hours	Yes
Dibasic sodium phosphate	Solid (oral) Solid (rectal)	1.9–3.8 g 3.8 g	¼ adult dose (5–10) ½ adult dose (≥10) ½ adult dose (>2)	Small and large intestines colon (rectal)	0.5–3 hours 2–15 min	Yes
Monobasic sodium phosphate	Solid (oral) Solid (rectal)	8.3–16.6 g 16.6 g	¼ adult dose (5–10) ½ adult dose (≥10) ½ adult dose (>2)	Small and large intestines Colon	0.5–3 hours 2–15 min	Yes
Sodium biphosphate	Solid (oral) Solid (rectal)	9.6–19.2 g 19.2 g	¼ adult dose (5–10) ¼ adult dose (≥10) ½ adult dose (>2)	Small and large intestines Small and large intestines	0.5–3 hours 2–15 min	Yes —
Hyperosmotic						
Glycerin	Suppository	3 g	1–1.5 g (<6)	Colon	0.25–1 hour	
Stimulants						
Anthraquinones	Solid	0.12–0.25 g	Not recommended (≤6)	Colon	8–12 hours	Yes
Aloe			0.04–0.08 g (6–8)			
Cascara sagrada	Fluidextract Aromatic Fluidextract Bark Extract Casanthranol	0.5–1.5 ml 2–6 ml 0.3–1.0 g 0.2–0.4 ml 0.03–0.09 ml	¼ adult dose (>2) ½ adult dose (2–12)	Colon —	6–8 hours —	Yes —

Table 6. continued

Agent	Dosage form	Daily dosage range: Adult	Daily dosage range: Pediatric (age in years)	Site of action	Approximate time required for action	Systemic absorption
Stimulants						
Danthron	Solid	0.075–0.15 g	Not recommended (<12)	Colon	8 hours	Yes
Senna	Powder	0.5–2.0 g	⅛ adult dose (>2)	Colon	6–10 hours	Yes
	Fluidextract	2.0 ml				
	Syrup	8.0 ml	¼ adult dose (1–6)			
	Fruit extract	3.4–4.0 ml	½ adult dose (6–12)			
	Suppository	1	½ adult dose (children over 60 lb)			
Sennosides A and B	Solid	0.012–0.036 g	0.0015–0.018 g 0.0015–0.1812 g	Colon	6–10 hours	—
Diphenyl methanes						
Bisacodyl	Tablet	0.005–0.015 g	0.005 g (>3)	Colon	6–10 hours	Yes
Phenolphthalein	Solid	0.03–0.27 g	Not recommended (<2) 0.015–0.020 g (2–6) 0.03–0.06 g (<6)	Colon	6–8 hours	Yes
Miscellaneous						
Castor oil	Liquid	15–60 ml	1–5 ml (<2) 5–15 ml (2–12)	Small intestines	2–6 hours	Yes

usate did not alter the incidence of constipation in a hospitalized geriatric population who received the drug for a 4-week period (17).

By facilitating the absorption of other poorly absorbed substances, such as danthron and mineral oil, the toxicity of the latter may be increased by concomitant administration of emollient laxatives (18, 19). A risk of hepatotoxicity exists when docusate is combined with danthron, although neither laxative by itself has been reported to cause this effect (20). It has been postulated that the detergent properties of docusate facilitates transport of other substances across cell membranes (21). Consequently, the FDA advisory review panel on nonprescription laxative, antidiarrheal, emetic, and antiemetic drug products recommended that these laxatives carry the following warning statement: "Do not take this product if you are presently taking a prescription drug or mineral oil" (16). Reports have indicated that daily use for 8 months or longer of preparations containing docusate sodium and oxyphenisatin acetate may produce chronic active liver disease with the attendant symptoms, including jaundice (22–25). As a result of these reports and other recommendations, laxatives containing oxyphenisatin acetate are no longer commercially available (26).

Patients with abdominal hernia, severe hypertension, or cardiovascular disease as well as those immediately post partum should not strain to defecate; neither should those who are about to undergo or have undergone surgery for hemorrhoids or other anorectal disorders. An emollient or fecal-softening laxative is indicated in such cases.

Lubricant Laxatives

Liquid petrolatum and certain digestible plant oils, such as olive oil, soften fecal contents by coating them and thus preventing colonic absorption of fecal water. Emulsified products are used to increase palatability. There is little difference in their cathartic efficacy, although emulsions of mineral oil penetrate and soften fecal matter more effectively than nonemulsified preparations. Liquid petrolatum is useful when it is used judiciously in cases that require the maintenance of a soft stool to avoid straining (after a hemorrhoidectomy or abdominal surgery, or in cases of hernia, aneurysm, hypertension, myocardial infarction, or cerebrovascular accident). However, routine use in these cases is probably not indicated. Stool softeners such as docusate sodium are probably better agents for these conditions.

The side effects and toxicity of mineral oil are associated with repeated and prolonged use. Significant absorption of mineral oil may occur, especially if emulsified products are used. The oil droplets may reach the mesenteric lymph nodes and may also be present in the intestinal mucosa, liver, and spleen, where they elicit a typical foreign body reaction.

Lipid pneumonia may result from the oral ingestion and subsequent aspiration of mineral oil, especially when the patient reclines. Therefore, it should not be taken at bedtime nor administered to debilitated patients. The pharynx becomes coated with the oil, and droplets gain access to the trachea and the posterior part of the lower lobes of the lungs.

The role of mineral oil in the absorption of fat-soluble nutrients is controversial, but there is apparently

sufficient evidence to consider this effect significant. Absorption of vitamins A, D, E, and K may be impaired. Impaired vitamin D absorption may affect the absorption of calcium and phosphates.

In addition, mineral oil should not be taken with meals because it may delay gastric emptying. Mineral oil should not be given to pregnant patients since it can decrease the availability of vitamin K to the fetus. Those patients receiving oral anticoagulants should not receive mineral oil for the same reason (27).

Large doses of mineral oil may cause the oil to leak through the anal sphincter. This leakage may produce anal pruritus (pruritus ani), hemorrhoids, cryptitis, and other perianal disease and can be avoided by reducing the dose, dividing the dose, or using a stable emulsion of mineral oil. Prolonged use should be avoided. Because of the tendency of surfactants to increase the absorption of "nonabsorbable" drugs, mineral oil should not be taken with emollient fecal softeners. Mineral oil is not recommended for use in the very young or the elderly because of the greater possibility of aspiration into the lungs resulting in lipid pneumonia (28).

Saline Laxatives

The active constituents of saline laxatives are relatively nonabsorbable cations and anions such as magnesium and sulfate ions. Sulfate salts are considered to be the most potent of this category of laxatives. The wall of the small intestine, acting as a semipermeable membrane to the magnesium, sulfate, tartrate, phosphate, and citrate ions, retains the highly osmotic ions in the gut. The presence of these ions draws water into the gut causing an increase in intraluminal pressure. The increased intraluminal pressure exerts a mechanical stimulus that increases intestinal motility. However, reports suggest that different mechanisms, independent of the osmotic effect, also are responsible for the laxative properties of the salts. Saline laxatives have a complex series of actions, both secretory and motor, on the GI tract. For example, the action of magnesium sulfate on the GI tract is similar to that of cholecystokinin-pancreozymin. There is evidence that this hormone is released from the intestinal mucosa when saline laxatives are administered (29). This release in turn favors intraluminal accumulation of fluid and electrolytes. However, attempts at measuring cholecystokinin levels in patients before and after ingestion of magnesium-containing laxatives failed to demonstrate a change in serum cholecystokinin levels (30). One report indicated that magnesium sulfate is still useful in emergency situations as a cathartic (31).

Saline laxatives are indicated for use only in acute evacuation of the bowel (preparation for endoscopic examination and elimination of drugs in suspected poisonings) and in ridding the gut of blood in conditions such as hepatic coma. Saline laxatives do not have a place in the long-term management of constipation.

In cases of food or drug poisoning, the saline laxatives are sometimes used in purging doses. Magnesium sulfate is recommended except in cases of depressed CNS activity or renal dysfunction (32).

There are cases in which the unwise choice of a saline laxative results in serious side effects. As much as 20% of the administered magnesium ion may be absorbed from magnesium salts. If renal function is normal, the absorbed ion is excreted so rapidly that no change in the blood level of the ion can be detected. If the renal function is impaired, or if the patient is a newborn or elderly, toxic concentrations of the magnesium ion could accumulate in the extracellular body fluids. In addition, hypotension, muscle weakness, and EKG changes may indicate a toxic effect of magnesium. Magnesium exerts a depressant effect on the central nervous system and neuromuscular activity.

Phosphate salts are available both in oral and rectal dosage forms. The normal oral dose contains 96.5 mEq of sodium and therefore should be administered with caution to patients on sodium-restricted diets. The use of phosphate salts in children under the age of 2 can result in hypocalcemia, tetany, hypernatremia dehydration, and hyperphosphatemia (33, 34). When given in an enema, up to 10% or more of its sodium content may be absorbed. Barium enema preparations and elimination of fecal impaction are indications for the rectal use of phosphates. Cathartics that contain sodium may be toxic to individuals with edema and congestive heart disease. Since dehydration may occur from the repeated use of hypertonic solutions of saline cathartics, they should not be used by those who cannot tolerate fluid loss and should be followed by at least 1 full glass of water in normal patients to prevent dehydration.

Hyperosmotic Laxatives

Glycerin suppositories are available for infants and adults and usually produce a bowel movement within 30 minutes. Glycerin for many years was the main suppository used for lower bowel evacuation. In infants, the physical manipulation usually will initiate the reflex to defecate, and because of this property, adverse reactions and side effects are minimal (35). The laxative effect of glycerin suppositories is due to the combination of glycerin's osmotic effect with the local irritant effect of sodium stearate. However, rectal irritation may occur with its use. The customary rectal dosages of glycerin considered to be safe and effective for adults and children older than 6 years are 3 g as a suppository or 5–15 ml as an enema. For infants and children under 6 years of age, the dose is 1–1.5 g as a suppository or 2–5 ml as an enema (16). Claims have been made that suppositories may be equal in effectiveness to enemas (37).

Stimulant Laxatives

A comprehensive review of stimulant laxatives has been reported, and the structure–activity relationships of the anthraquinone or emodin-containing laxatives have been investigated (38–40). Stimulant laxatives increase the propulsive peristaltic activity of the intestine by local irritation of the mucosa or by a more selective action on the intramural nerve plexus of intestinal smooth muscle, thus increasing motility. Depending on the laxative, the site of action may be the small intestine, the large intestine, or both. Intensity of action is proportional to dosage, but individually effective doses vary. All stimulant laxatives produce gripping, increased mucus secretion, and, in some people, excessive evacuation of fluid.

Listed doses and dosage ranges are only guides to the correct individual dose. Stimulant laxatives should be used with caution when symptoms of appendicitis (abdominal pain, nausea, and vomiting) are present and should not be used at all when the diagnosis of appendicitis is made.

Stimulant laxatives are effective but should be recommended cautiously because they may produce undesirable and sometimes dangerous side effects (15). This property becomes more important when the agents are abused. It has been said that of all laxative products available, stimulant laxatives are the most widely abused (41). Chronic abuse can lead to "cathartic colon," a poorly functioning colon resembling ulcerative colitis.

In general, stimulant laxatives are not recommended as initial therapy in patients with constipation, and they should never be used for more than 1 week of regular treatment. The dose should be within the dosage range indicated as safe and effective (Table 6). These laxatives do not necessarily provide a good stimulus for the body to return to normal function. Major hazards of stimulant laxatives are severe cramping, electrolyte and fluid deficiencies, enteric loss of protein and malabsorption resulting from excessive catharsis, and hypokalemia. Since the intensity of stimulant laxative activity is proportional to the dose employed, if the dose is large enough, any of the stimulant laxatives can produce these unwanted side effects.

Stimulant laxatives, such as castor oil and bisacodyl, frequently are used before radiologic examination of the GI tract and before bowel surgery. Bisacodyl also is used orally or rectally instead of an enema for emptying the colon before proctologic examination.

Stimulant laxatives are classified according to their structure and activity.

Anthraquinones Anthraquinone laxative agents, also called anthracene laxatives, include aloe, cascara sagrada, danthron, and rhubarb. Also included in this category are senna, aloin, casanthranol, and frangula. The drugs of choice in this group are the cascara and senna compounds. Neither rhubarb, which contains an astringent (tannin), nor aloe, or aloin, which are very irritating, should be recommended. The properties of each of the anthraquinone laxatives vary, depending on the anthraquinone content and the speed of liberation of the active principles from their glycosidic combinations. The anthraquinone glycosides are hydrolyzed by colonic bacteria into active compounds. Crude drug formulation also may contain active constituents not found in extractive preparations or more highly purified compounds.

The precise mechanism by which peristalsis is increased is unknown. The cathartic activity of anthraquinones is limited primarily to the colon, which is reached by direct passage. Bacterial enzymes are partly responsible for the hydrolysis of the glycosides in the colon, making the drug more readily absorbed. Anthraquinones usually produce their action 6–12 hours after administration but may require up to 24 hours.

The active principles of anthraquinones are absorbed from the GI tract and subsequently appear in body secretions, including human milk. However, the practical significance of this finding in nursing infants is controversial.

After taking a senna laxative, postpartum women reported a brown discoloration of breast milk and subsequent catharsis of their nursing infants. A follow-up study indicated that the amount of senna laxative principles in breast milk was inadequate to stimulate defecation in the child (42). Another study with constipated postpartum breast-feeding women receiving a senna laxative reported that 17% of their infants experienced diarrhea (43).

Chrysophanic acid, a component of rhubarb and senna excreted in the urine, colors acidic urine yellowish-brown and alkaline urine reddish-violet.

The prolonged use of anthraquinone laxatives, especially cascara sagrada, can result in a melanotic pigmentation of the colonic mucosa, which is usually found on sigmoidoscopy or rectal biopsy. The shortest time observed for the appearance of melanosis coli in patients taking an anthraquinone cathartic in the presence of fecal stasis was 4 months and the longest was 13 months. In almost all cases, melanosis disappears within 5–11 months after discontinuation of the drug (44). Melanosis coli is virtually always due to prolonged use of anthraquinone laxatives (45). Pigment-containing macrophages appear in the mucosa, but staining reactions indicate that the pigment is not melanin but has many characteristics of lipofuscin. It may be a combination of a pigment of this type and either anthraquinone or one of its breakdown products. There is little evidence to suggest that laxatives other than anthraquinones lead to this pathologic feature.

The liquid preparations of cascara sagrada (fluidextracts) are more reliable than the solid dosage forms (extract and tablet). Aromatic cascara fluidextract is less active and less bitter than cascara sagrada fluidextract. This is reflected by the recommended dosages (Table 6). Magnesium oxide, used in the preparation of the former, removes some of the bitter and irritating principles from the crude drug.

Preparations of senna are more potent than those of cascara and produce considerably more gripping. Those that contain the crystalline glycosides of senna are more stable and reliable, and cause less gripping then those made from the crude drug. This difference is important in making a standardized senna product the logical choice among anthracene laxatives (46).

Danthron (1,8-dihydroxyanthraquinone), a breakdown product of the glycosides of senna, is a free anthraquinone rather than a glycoside. Its action, use, properties, and limitations are similar to those of the natural anthraquinone drugs. Like the glycosides, its site of action is the colon. Unlike the naturally occurring agents, it is partly absorbed from the small intestine, and much of the absorbed drug is metabolized by the liver. The metabolites are excreted by the kidneys, sometimes causing a pink to red discoloration of the urine.

Diphenylmethane Laxatives

The most common diphenylmethane laxatives are bisacodyl and phenolphthalein.

Bisacodyl Bisacodyl was introduced as a cathartic as a result of structure-activity studies of phenolphthalein-related compounds. Practically insoluble in water or a saline medium, bisacodyl exerts its action in the colon on contact with the mucosal nerve plexus. Stimulation is segmented and axonal, producing contractions of the entire colon. Its action is independent of intestinal tone, and the drug is minimally absorbed systemically (approximately 5%) (27). Action on the small intestine is negligible. A soft, formed stool usually is produced 6–10 hours after oral administration and 15–60 minutes after rectal administration. Bisacodyl tablets are enteric coated to prevent irritation of the gastric lining and therefore should not be broken, chewed, or administered with alkaline materials such as antacid products.

The tablet and suppository combination have been recommended for cleaning the colon before and after surgery and before X-ray examination. Bisacodyl increases ileostomy water output and is effective in patients with colostomies and reduces or eliminates the need for irrigations (47). No systemic or adverse effects on the liver, kidney, or hematopoietic system have been observed following its administration. Side effects occur primarily from purgative action and include metabolic acidosis or alkalosis, hypocalcemia, tetany, and loss of enteric protein and malabsorption (48). Bisacodyl has not been detected in the milk of nursing women. The suppository form may produce a burning sensation in the rectum.

Phenolphthalein This drug exerts its stimulating effect mainly on the colon, but the activity of the small intestine may be increased as well. Its exact mechanism of action is not known but phenolphthalein appears to alter multiple steps of the absorptive process. It is usually active 6–8 hours after administration.

Phenolphthalein is effective in small doses and is tasteless, making it desirable for marketing in candy and chewing gum forms. When ingested, it passes through the stomach unchanged and is dissolved by the bile salts and the alkaline intestinal secretions. As much as 15% of the dose is absorbed, and the rest is excreted unchanged in the feces. Some of the absorbed drug appears in the urine, which is colored pink to red if it is sufficiently alkaline. Similarly, the drug excreted in the feces causes a red coloration if the feces are sufficiently alkaline (soap suds enemas). This effect may alarm people who are not aware of this property.

Part of the absorbed phenolphthalein is excreted back into the intestinal tract with the bile. The resulting enterohepatic cycle may prolong the action of phenolphthalein for 3–4 days. Since bile must be present for it to be effective, phenolphthalein is ineffective in relieving constipation associated with obstructive jaundice.

Phenolphthalein is usually nontoxic. However, at least two types of allergic reactions may follow the use of phenolphthalein. In susceptible individuals, a large dose may cause diarrhea, colic, cardiac and respiratory distress, or circulatory collapse. The other reaction is a polychromatic rash that ranges from pink to deep purple. The eruptions may be pinhead-sized or as large as the palm of the hand. Itching and burning may be moderate or severe. If the rash is severe, it may lead to vesication and erosion, especially around the mouth and genital areas. Other skin reactions, including toxic epidermal necrosis and bullous eruptions, may occur and are related to sunlight exposure (49).

Osteomalacia due to impaired absorption of vitamin D and calcium is one untoward effect that has been attributed to excessive phenolphthalein ingestion (49, 50). Phenolphthalein abuse can mimic Bartter's syndrome by inducing juxtaglomerular cell hyperplasia with secondary aldosteronism. This is characterized by hypokalemic alkalosis and marked renin increase in the absence of hypertension (51).

Miscellaneous: Castor Oil

The laxative action of castor oil is due to ricinoleic acid, which is produced when castor oil is hydrolyzed in the small intestine by pancreatic lipase. Its mechanism of action is unknown. However, its laxative effect depends upon cyclic adenosine monophosphate mediated fluid secretion and not from increased peristalsis due to the irritant effect of ricinoleic acid (52).

Castor oil, a glyceride, may be absorbed from the GI tract and is probably metabolized like other fatty acids. Because the main site of action is the small intestine, its prolonged use may result in excessive loss of fluid, electrolytes, and nutrients. Castor oil is most effective when administered on an empty stomach and produces an evacuation within 2–6 hours after ingestion. Because of its unpleasant taste it should be administered with fruit juices or carbonated beverages. Although used in situations requiring a thorough evacuation of the GI tract, it is seldom used routinely for constipation.

Dosage Forms

Laxative products are available in a wide array of dosage forms. Most of these are given orally. Variety in dosage forms probably yields the most benefits when laxatives are needed in pediatric or geriatric patients. However, by no means are all of the available dosage forms necessary for effective laxative action. Many of the dosage forms enhance patient acceptability and perhaps, make laxative use pleasant. Laxatives available as chewing gum, effervescent granules, and chocolate tablets may certainly be associated with pleasantness but may not always be thought of as drug products because of this. Consequently, patients may use them indiscriminately. It is important to keep this fact in mind especially when considering laxative abuse.

Enemas and suppositories are dosage forms used extensively for laxative administration. Enemas are used routinely to prepare patients for surgery, child delivery, radiologic examination, and in certain cases of constipation. The enema fluid determines the mechanism by which evacuation is produced. Tap water and normal saline create bulk by an osmotic volume effect; vegetable oils lubricate, soften, and facilitate the passage of hardened fecal matter; soapsuds produce defecation by their irritant action. There have been reports of rectal irritation that has lasted as long as 3 weeks after soap enemas. In addition, there have been reports of anaphylaxis, rectal gangrene, and serious fluid loss secondary